ACUTE EXACERBATIONS of COPD (AE-COPD) :

The Belgian perspective

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Yvan Valcke MD PhD
AZ Maria Middelares
Sint-Niklaas

ACUTE EXACERBATIONS of COPD (AE-COPD)

- Treatment of AECB
- Role of antibiotics in infectious AECB
- Belgian resistance data
- Belgian AB-recommendations

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INFECTIOUS AE-COPD

Therapeutic interventions

- **Drainage enhancing and anti-inflammatory drugs :**
  - **bronchodilators**
  - **systemic corticosteroids (not inhaled steroids !)**

2. Oxygen, in hypoxemic patients.

3. Mucolytic agents, methylxanthines, physiotherapy : no proven benefit !!

4. Antibiotics: controversial !!

GOLD guidelines Am J Respir Crit Care Med 2001;163:1256
Ann Intern Med 2001; 134: 595

ACUTE EXACERBATIONS of COPD (AE-COPD)

- **Treatment of AECB**
- ***Role of antibiotics in infectious AECB***
- **Belgian resistance data**
- **Belgian AB-recommendations**

Infectious AE-COPD : role of bacteria

- Prospective, longitudinal cohort study
- n = 81 ; t = 56 months
- sputum culture with molecular typing :
  monthly
  during exacerbation

Acquisition of a new strain of a pathogenic bacterial species in a COPD patient without preexisting immunity to the strain, significantly increases the risk of an exacerbation

Sethi et al. N Engl J Med 2002;347:465-471

DO ANTIBIOTICS WORK in AE-COPD ? (1)

- **11 randomized placebo-controlled studies :**

  AB: beneficial in type I + II exacerbations

  resolution of symptoms
  return of peak flow rate

  AB: no benefit to prevent exacerbations

- **narrow spectrum AB most commonly evaluated:** ***amoxicilline, co-trimoxazole, tetracycline***

Ann Intern Med. 2001;134:600

DO ANTIBIOTICS WORK in AE-COPD ? (2)

- No studies demonstrate superiority of outcome with newer broad-spectrum AB
- Studies done before emergence of multi-drug resistant pathogens (PRSP)
- No studies relate the beneficial AB effect to severity of lungfunction-impairment in COPD patients

Ann Intern Med. 2001;134:600

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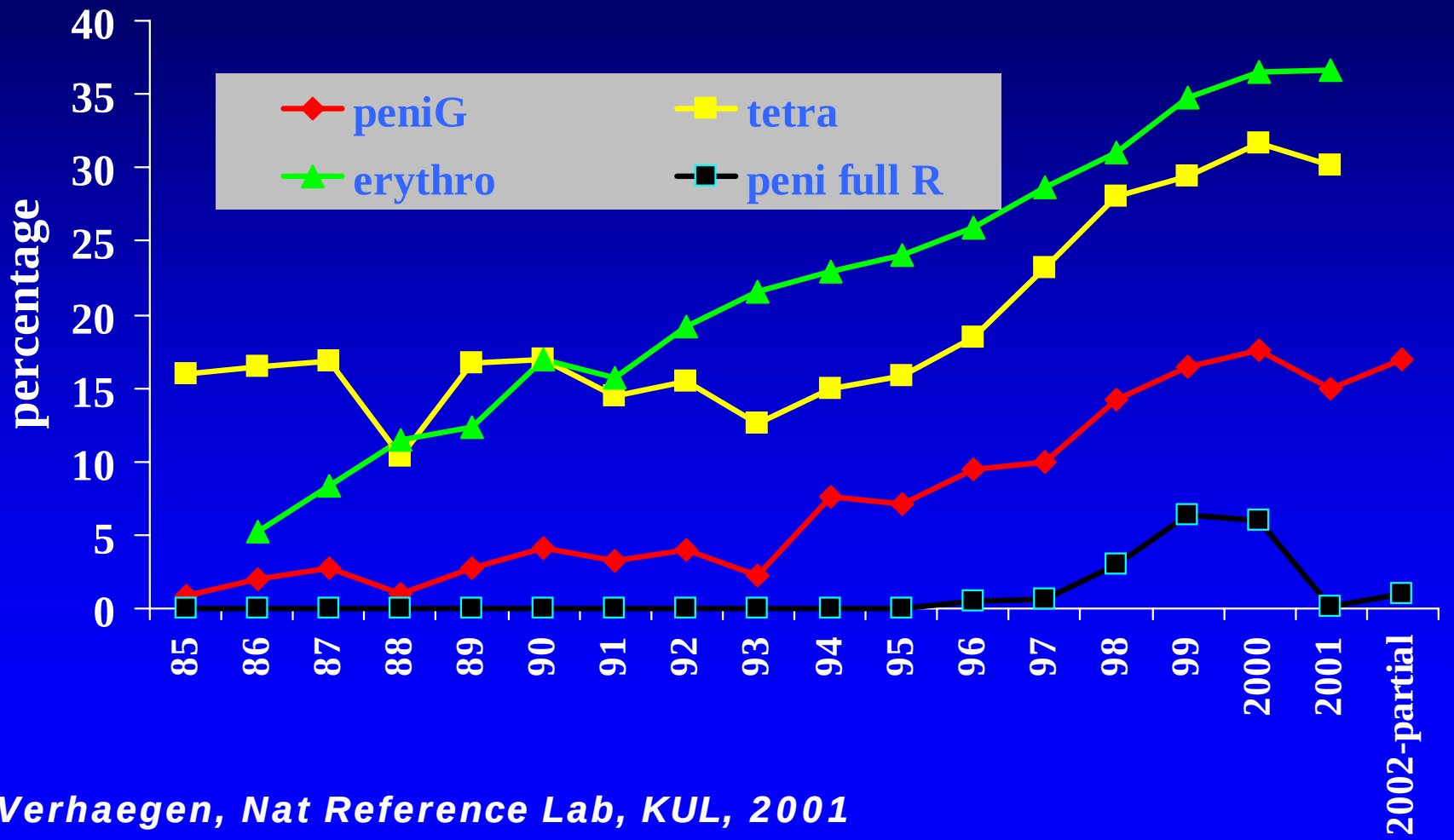
Evolution of *S. pneumoniae* resistance rates in Belgium



J. Verhaegen, Nat Reference Lab, KUL, 2001

Antibiotic resistance: *S. pneumoniae*

	2001 invasive n=1434 (1)	2000 - 2001 respiratory n=314 (2)	1999 - 2000 respiratory n=637 (3)
penicillin G	15,0 %	21,0 %	18,2 %
(I + R)	14,8 + 0,2	10,8 + 10,2	ND
cefotaxime	0,5 %	7,3 %	ND
erythromycin	36,6 %	30,3 %	38,5 %
tetracycline	30,2 %	38,5 %	33 %
levofloxacine	0,1 %	2,5 %	1,1 %

1: J. Verhaegen. Nat Reference Laboratory 2001
2: R. Vanhoof et al. ECCMID 2002; Poster P451
3: J. Verhaegen, et al. Telithromycin study ICAAC 2000

Penicillin-resistant *S. pneumoniae*

- **invasive strains :**

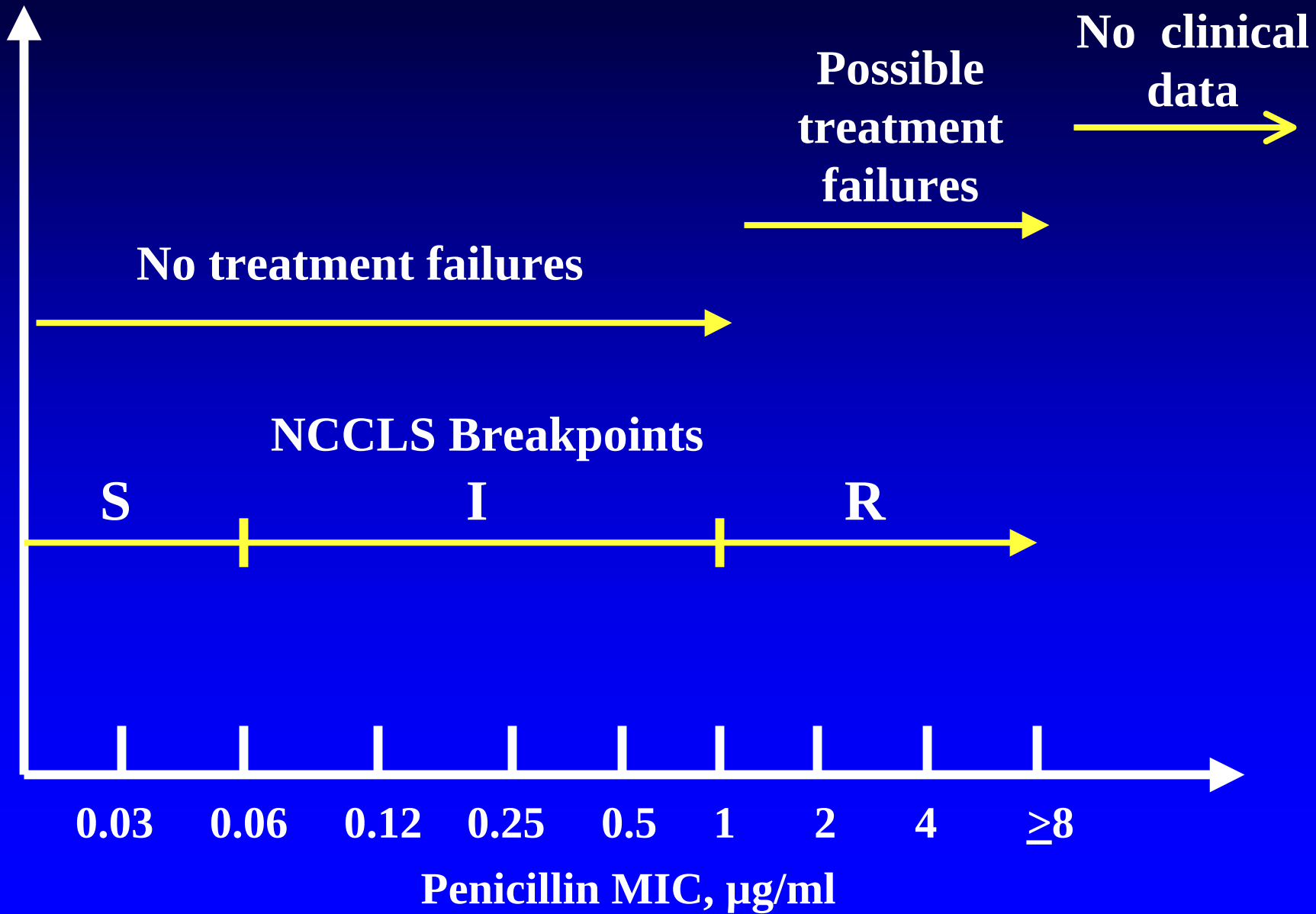
  reduced penicillin susceptibility : 15 %

  - **intermediate resistance (Peni-I) : 14,8 %**
  - **high-level resistance (Peni-R) : 0,2 %**

  Surveillance Pneumokokkeninfecties België, 2001

- **resistance not due to b-lactamase production but linked to altered Penicillin Binding Proteins**

Pneumococcal RTI : Peni-Resistance *vs.* Clinical Outcomes



Clinical significance of Peni-resistance in Pneumococcal RTI

Conclusions

- **Beta-lactams :**

  - still effective in pneumococcal RTI (MIC ≤ 2mcg/ml)

  - should be adequately dosed :
  to obtain T>MIC: > 40% of dosing interval
  to prevent further emergence of resistance

- **New « respiratory » AB : not needed in first choice**

Arch Intern Med 2000;160:1399

Macrolide-resistant *S. pneumoniae*

RESISTANCE MECHANISMS

- **BELGIUM**
  - methylation of ribosomal RNA (erm B gene): 92 %
  - efflux (mef E gene): 3 %
  - both (erm B gene + mef E gene): 5 %

- **USA**
  - mostly efflux mechanism

MIC efflux << MIC ribosomal :
In Belgium: macrolide resistance = treatment failure

J Antimicrob Chemother 2000; 45: 119-121.
Clin Microbiol Infect 2000; 6: 661-669.

Macrolide and tetracycline resistant *S. pneumoniae*

- **erythromycin resistance : 36.6 %**

  complete cross-resistance between all macrolides in > 90% of erythromycin-resistant strains; no cross-resistance with telithromycin

- **tetracycline resistance : 30.2%**

J. Verhaegen, Nat Reference Lab, KUL, 2001

Antibiotic resistance: *H. influenzae*

- M. Delmée et al. Acta clin Belg 1996; 51: 237-243.
  - beta-lactamase-positive : 16,7 %
  - bla-neg ampi R: 1,1 %
- P. De Mol unpublished results 2000 (n=474)
  - beta-lactamase-positive: 16,0 %
  - bla-neg amp R: 3,0 %

Antibiotic resistance: *M. catarrhalis*

- **P. De Mol. unpublished data 2000 (n=164 clinically significant isolates)**

  beta-lactamase positive: 75 %

- **remain susceptible to amoxi-clav, cephalo 2, macrolides and fluoroquinolones**

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BELGIAN COPD – GUIDELINES
Premises

- In Belgium, presently available macrolides, azalides and older quinolones offer inadequate coverage of S. pneumoniae

- High betalactam dosages are preferred :
  - ↓ resistance selection
  - > 40% time>MIC for peni-I/R S. pneumoniae

- First generation cephalosporins (also cefaclor) are less active than amoxicillin and cefuroxim against peni-I/R S. pneumoniae

Infectious AE-COPD :

Belgian recommendations (1)

- **Amoxi-Clav 875mg q8-12h po / 5-10 d**

  or

- **Cefuroxime-axetil 500mg q8-12h po / 5-10 d**

Consensus vergadering RIZIV 17 / 10 / 2000

Infectious AE-COPD :

Belgian recommendations (2)

- **Amoxi-Clav 1g q6h iv**

  or

- **Cefuroxime 1.5g q8h iv**

Consensus vergadering RIZIV 17/10/2000

Role of new « respiratory » antimicrobials released in Belgium

- New Fluoro-quinolones (NFQ)
- Ketolide (Telithromycin)

NFQ's released in Belgium

Name	Use	Dose
Levofloxacin (Tavanic)	PO IV	500 mg OD/BID
Moxifloxacin (Avelox/ Proflox)	PO	400 mg OD

Concentration dependent, rapidly bactericidal

NFQ in RTI

PRO'S

Anti-bacterial activity and clinical efficiency

- Respiratory bacteria and atypicals
- Not related to peni- and macrolide-resistance

Pharmacokinetic advantages

- Bio-equivalency po - iv
- Quick sequential therapy
- OD - BID
- High tissue disposition

NFQ in RTI

CON'S

- Safety / Unexpected toxicity (PMS)
- Commercial benefits =
  flu-like syndroms, URTI, AECB
- Massive use = resistance
  among respiratory pathogens
  among commensal gut-flora

DO NFQ WORK in AECB ?

- No placebo controlled studies with NFQ
- Several studies show equal, but not superior, clinical success compared with standard regimens
- Some studies show improved bacteriological eradication rates with moxifloxacin and levofloxacin (mainly *H. influenzae*)
- No studies compare NFQ's

DO WE NEED NFQ in AE-COPD ?

Not as first choice : cfr.:

- Adequately dosed beta-lactams effective
- No superior outcome with NFQ
- Risk of over- and misuse of NFQ and hence resistance

Yes as alternative :

- IgE mediated beta-lactam allergy
- failure or major intolerance of beta-lactams
- proven penicillin-resistant pneumococci

KETOLIDES

Name	Use	Dose
Telithromycin (Ketek)	PO	800 mg OD (= 2x400 mg tabl.)

Concentration dependent, bactericidal activity

TELITHROMYCIN in RTI

PRO'S

Anti-bacterial activity and clinical efficiency

- *S. pneumoniae* and atypicals
- Not related to peni- and macrolide-resistance

Pharmacokinetic advantages

- OD
- High tissue disposition

TELITHROMYCIN in RTI

CON'S

- Weak anti – *H. influenzae* activity
- Only orally
- Commercial benefits =
  flu-like syndroms, URTI, AECB: resistance
- Studies in peni- and erythro-R RTI's needed
- Further data on cardiotoxicity (QTc) needed

AB treatment for infectious AE-COPD : conclusions (1)

1. AB only useful in patients with more severe types of exacerbation (Anthonisen criteria and baseline FEV1 < 50%)

2. Choice of antibiotic determined by most likely bacterial pathogens, local resistance data and clinical experience

AB treatment for infectious AE-COPD : conclusions (2)

3. Amoxicillin/clav and cefuroxime remain first choice

4. NFQ are a valid alternative: but to avoid overuse, limited to IgE-mediated beta-lactam allergic patients, clinical failures and major intolerance with beta-lactams, and proven PRSP

5. The role of telithromycin is debatable because of limited anti-H.influenzae activity